UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/575,554	05/22/2000	Brett P. Monia	ISPH-0463	1277

7590 07/12/2002

Law Offices of Jane Massey Licata
66 E Main Street
Marlton, NJ 08053

EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 14

Application Number: 09/575,554

Filing Date: May 22, 2000

Appellant(s): Monia et al

Jane Massey Licata

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 20, 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct. It is noted that the obviousness type double patenting rejection is withdrawn in view of the terminal disclaimer filed February 11, 2002.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1 and 7-20 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

4,871,838	BOS et al	10-1989

Daaka et al. "Target dependence of antisense oligodeoxynucleotide inhibition of c-Ha-ras p21 expression and focus formation in T24-transformed NIH3T3 cells." Oncogene Research, vol. 5, No. 4 (1990), pp. 267-275.

Hall et al., "Human N-ras: cDNA cloning and gene structure." Nucleic Acids Research, vol. 13, no. 14 (1985), pp. 5255-5268.

Saison-Behmoaras et al. "Short modified antisense oligonucleotides directed against Ha-ras point mutation induce selective cleavage of the mRNA and inhibit T24 cells proliferation." EMBO J. Vol. 10, (1991) pp. 1111-1118.

Uhlmann et al. "Antisense oligonucleotides: a new therapeutic principle.", Chemical Reviews, vol. 90, no. 4 (June 1990), pp. 543-584.

Agrawal et al. "Site-specific excision from RNA by RNAse H and mixed phosphate backbone oligodeoxynucleotides" Proc. Natl. Acad. Sci. USA, vol. 87 (February 1990), pp. 1401-1405.

Inoue et al. "Sequence dependent hydrolysis of RNA using modified oligonucleotide splints and RNAse III." FEBS Letters, vol. 215, no. 2 (May 1987), pp. 327-330.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1 and 7-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos, Daaka et al., Hall et al (Nucleic Acids Res. 13(14):5255-5268) and Saison-Behmoaras et al., each in view of Uhlmann et al., Agrawal et al. and Inoue et al., and further in view of Smith.

Bos discloses antisense oligonucleotides to human H-ras and Ki-ras and to the specific regions of ras genes (codons 12 and 61) that are mutated in the activated forms of these genes (see Column 4, line 26 to Column 5, line 10). Bos teaches that the molecules

of the invention may be labeled and used in methods to detect the activated forms of ras, by either hybridizing to single-stranded genomic DNA fragments or to RNA isolated from cells or tissue to be tested. Hall teaches the sequence of N-ras from which the specific antisense molecules are derived as well as the importance of the mutations at codons 12 and 61 (page 5256, and page 5264, figure 4). Daaka et al. teach antisense molecules to the translation initiation codon site of the H-ras gene and the use of the antisense molecules to inhibit H-ras expression in and the growth of transformed 3T3 cells. Saison-Behmoaras et al. teach oligonucleotides that specifically hybridize to the codon 12 region of H-ras and methods of using the oligos to inhibit expression of the gene. Thus, the three primary references all provide teachings of oligonucleotides directed against the claimed regions of H-ras or Ki-ras and their use to inhibit expression of the gene and growth of transformed cells, or to detect the activated genes. The primary references do not teach oligos having phosphorothioate linkages, chimeric oligonucleotides containing runs of phosphodiester-linked oligodeoxynucleotides flanked by RNase H-resistant oligonucleotides, modifications to increase the affinity toward the target, the specific oligonucleotide sequences of the instant invention or the method of treating an animal by administering the oligonucleotides of the invention. Uhlmann et al. teach a wide variety of modifications to antisense oligonucleotide structures, including phosphorothioate backbone modifications and the use of 2'-modified ribonucleotides such as 2'-O-methyl nucleotides. Uhlmann et al. disclosed motivation for making oligos with these modifications to increase stability and decrease costs. They also disclosed that 2'-O-methyl modified oligonucleotides formed duplexes with RNA that were more thermostable

than DNA-RNA hybrids, thus suggesting that 2'-O-methyl oligos had increased affinity for their RNA targets. Inoue et al. and Agrawal et al. each teach the RNase H sensitivity or resistance of duplexes formed from RNA and various modified oligonucleotides. Agrawal discloses that phosphodiester and phosphorothioate backbones confer sensitivity to RNase H, whereas oligos with methylphosphonate and some other backbone structures confer resistance to RNase H. Inoue et al. disclosed chimeric antisense oligonucleotides containing resistant 2'-O-methyl residues flanking at least 4 deoxynucleotide residues. These molecules, after forming a duplex with complementary RNA, promoted specific cleavage by RNase H in the tetradeoxynucleotide region of the duplex. Smith et al. disclose the use of antisense oligonucleotides, with or without modified backbones, against oncogenes or genes that are differentially expressed in tumor cells, as a treatment for cancer. Thus, they disclose a method of treating cancer by administering appropriate antisense oligos to inhibit the growth of tumor cells or kill the tumor cells. Although the oligonucleotides that are claimed by specific sequence are not specifically disclosed in the art, the regions of the genes to which they are targeted are clearly taught in the art. The specific sequences would be derived by one of ordinary skill in the art making a variety of antisense oligonucleotides targeted at the taught regions. Thus, one of ordinary skill in the art would have known at the time the invention was made to modify the teachings of the primary references by making oligonucleotides that have modified backbones, stretches of deoxynucleotides that are sensitive to RNase H digestion and 2' modified ribose moieties as disclosed by Uhlmann et al., Agrawal et al. and Inoue et al., in order to obtain the advantages of increased stability, target affinity and target destruction taught by the

secondary references. One of ordinary skill in the art would further have known to use the oligos in methods of preventing expression of the ras gene, inhibiting tumor cell growth and treating an animal having an activated ras gene, and in methods of detecting different forms of the ras gene, as suggested by the primary references and Smith for the obvious advantages of slowing or stopping tumor growth and diagnosing the presence or absence of activated forms of the ras gene, which are linked to cancer. Therefore, the invention as a whole was *prima facie* obvious in the absence of evidence or secondary considerations to the contrary.

Further, Bos provides the requisite sequence information for Ki-ras. Hall provides the requisite sequence information for N-ras. Motivation is provided by several of these references. Saison-Behmoaras states "It has been found that 10-20% of human tumors have a mutation in one of the three ras genes (Ha-ras, Ki-ras, N-ras) leading to the production of p21 ras oncoproteins, which are thought to play an important role in the transformed phenotype (page 1111, column 1)". Here, Saison-Behmoaras discloses the equivalence of the three ras oncogenes and provides a strong and direct motivation to inactivate each of these genes, since they are found activated in 10-20% of human tumors. Saison-Behmoaras continues "In order to study the biological effects of ras expression in the context of molecular biology of ras-dependent pathway and to provide a rational basis for the development of antitumor drugs we are investigating the use of antisense oligonucleotides and their modified analogues, which upon hybridization to complementary mRNA sequences, interfere with translation and thus can be employed for sequence-specific control of gene expression. In an attempt to inhibit the expression of an

oncogene, application of antisense oligonucleotides has proved to be a powerful tool (page 1111, column 1 to column 2)". This quote demonstrates that Saison-Behmoaras provides a motivation to utilize antisense oligonucleotides to achieve the goal, as noted above, of inactivation of ras oncogenes, since antisense oligonucleotides were known to be a powerful tool to interfere with translation and gene expression of the ras oncogenes and since the antisense oligonucleotides could provide a rational basis for drug development. Further motivation is provided by Daaka, who states "The ras family of mammalian protooncogenes includes three members, termed Ha-ras, Ki-ras, and N-ras, that are likely to play a fundamental role in basic cellular functions based on their high degree of conservation throughout eukaryotic evolution (ref omitted). The amino acid sequence of the ras gene products all contain GTP-binding consensus regions and are thought to be localized to the inner surface of the plasma membrane (ref omitted). In mammals, ras proteins have been implicated in cellular proliferation (ref omitted) and terminal differentiation (ref omitted). Point mutations in ras oncogenes that alter the enzymatic properties and/or cause overexpression of the ras p21 oncoprotein may be causatively or closely linked ot the onset of some types of human tumors (refs omitted) (page 267, columns 1 and 2)." Daaka here also motivates the ordinary practitioner to inactivate mutated ras proteins, including any of the three equivalents, Ha-ras, Ki-ras or N-ras. Daaka also teaches the use of antisense methodologies to perform this inactivation (page 267, column 2 to page 268, column 1). Bos et al also motivates the inactivation of the ras oncogene, though Bos does not suggest an antisense mechanism " The human gene family consists of three members: the H-ras, K-ras and the N-ras gene (1) These genes

code for related proteins of 21kD, which are located at the inner face of the cell membrane (36) and are thought to be involved in transducing signals from cell surface receptors to their intracellular targets (37). A significant portion of tumor cell lines and fresh tumor tissue has been found to possess an activated ras gene. Such genes are characterized by their ability to induce oncogenic transformation of mouse 3T3 cells. In most cases so far analyzed the activation is due to a point mutation in the 12th or 61st codon of a ras gene resulting in a single amino acid substitution in the gene product (column 1, lines 14-26)". These three references each note the linkage and potential causative nature of ras oncogenes with human tumors. Each reference discloses that three different, but functionally and structurally equivalent ras oncogenes termed Ha-ras, Ki-ras and N-ras are involved in human tumors. Saison-Behmoaras and Daaka explicitly motivate the inactivation of these proteins by antisense mechanisms to inhibit tumor formation and growth. These references thus provide explicit motivation for the ordinary practitioner to inactivate Ki-ras, Ha-ras and N-ras in order to inhibit tumor formation and growth.

(11) Response to Argument

Introduction

In order to understand the issues in this application, the underlying technology will be briefly discussed. The claimed invention is drawn to "antisense oligonucleotides" This invention is based on nucleic acid hybridization, which is a process where one nucleic acid strand interacts with a second nucleic acid strand to form a double helix structure of two interacting strands in a sequence dependent

manner. That is, the double helix will only form where a first nucleic acid strand is complementary in the specific order of the four nucleotides, A, C, G and T with the second nucleic acid strand. For example, the sequence 5'-AAACCC-3' would interact with the sequence 5'-GGGTTT-3' to form a double helix as shown below:

5'-AAACCC-3'
3'-TTTGGG-5'

This specific interaction has been widely used for to inhibit the expression of particular nucleic acids for the past twenty five years.

Prima facie case

Appellant argues that the rejection fails to make a prima facie case of obviousness. Appellant first argues that the cited prior art fails to teach or suggest all the limitations of the claims and fails to provide motivation to make the rejection. Appellant has not identified specific limitation which is missing in the rejection.

Motivation and teaching of every limitation

As noted in the rejection, Bos teaches antisense oligonucleotides which are targeted to K-Ras (see column 4, lines 26-37, where Bos teaches a list of exemplary oligonucleotides). Bos further teaches targeting the antisense oligonucleotide to position 12 (see column 3, line 28). Saison-Behmoaras states "It has been found that 10-20% of human tumors have a mutation in one of the three ras genes (Ha-ras, Ki-ras, N-ras) leading to the production of p21 ras oncoproteins, which are thought to play an important role in the transformed phenotype (page 1111, column 1)". Here, Saison-Behmoaras discloses the equivalence of the three ras oncogenes and provides a strong and direct motivation to inactivate each of these genes, since they are found activated in

10-20% of human tumors. Saison-Behmoaras continues "In order to study the biological effects of ras expression in the context of molecular biology of ras-dependent pathway and to provide a rational basis for the development of antitumor drugs we are investigating the use of antisense oligonucleotides and their modified analogues, which upon hybridization to complementary mRNA sequences, interfere with translation and thus can be employed for sequence-specific control of gene expression. In an attempt to inhibit the expression of an oncogene, application of antisense oligonucleotides has proved to be a powerful tool (page 1111, column 1 to column 2)". This quote demonstrates that Saison-Behmoaras provides a motivation to utilize antisense oligonucleotides to achieve the goal, as noted above, of inactivation of ras oncogenes, since antisense oligonucleotides were known to be a powerful tool to interfere with translation and gene expression of the ras oncogenes and since the antisense oligonucleotides could provide a rational basis for drug development.

Further motivation is provided by Daaka, who states "The ras family of mammalian protooncogenes includes three members, termed Ha-ras, Ki-ras, and N-ras, that are likely to play a fundamental role in basic cellular functions based on their high degree of conservation throughout eukaryotic evolution (ref omitted). The amino acid sequence of the ras gene products all contain GTP-binding consensus regions and are thought to be localized to the inner surface of the plasma membrane (ref omitted). In mammals, ras proteins have been implicated in cellular proliferation (ref omitted) and terminal differentiation (ref omitted). Point mutations in ras oncogenes that alter the enzymatic properties and/or cause overexpression of the ras p21 oncoprotein may be

causatively or closely linked ot the onset of some types of human tumors (refs omitted) (page 267, columns 1 and 2)." Daaka here also motivates the ordinary practitioner to inactivate mutated ras proteins, including any of the three equivalents, Ha-ras, Ki-ras or N-ras. Daaka also teaches the use of antisense methodologies to perform this inactivation (page 267, column 2 to page 268, column 1). Bos et al also motivates the inactivation of the ras oncogene, though Bos does not suggest an antisense mechanism " The human gene family consists of three members: the H-ras, K-ras and the N-ras gene (1) These genes code for related proteins of 21kD, which are located at the inner face of the cell membrane (36) and are thought to be involved in transducing signals from cell surface receptors to their intracellular targets (37). A significant portion of tumor cell

lines and fresh tumor tissue has been found to possess an activated ras gene. Such genes are characterized by their ability to induce oncogenic transformation of mouse 3T3 cells. In most cases so far analyzed the activation is due to a point mutation in the 12th or 61st codon of a ras gene resulting in a single amino acid substitution in the gene product (column 1, lines 14-26)".

These three references each note the linkage and potential causative nature of ras oncogenes with human tumors. Each reference discloses that three different, but functionally and structurally equivalent ras oncogenes termed Ha-ras, Ki-ras and N-ras are involved in human tumors. Saison-Behmoaras and Daaka explicitly motivate the inactivation of these proteins by antisense mechanisms to inhibit tumor formation and

growth. These references thus provide explicit motivation for the ordinary practitioner to inactivate Ki-ras in order to inhibit tumor formation and growth.

The references direct the practitioner to codon 12 and 61 mutations and the 5' or 3' UTR of Ki-ras because Saison-Behmoaras states "In the ras gene family, activation of the protooncogene to form the oncogene is due to point mutations, most often in the 12th and 61st codons (page 1111, column 2)". This statement is generic to all three ras gene family members, including Ki-ras. This statement also directs the ordinary practitioner to design antisense oligonucleotides at these two sites, which is completely constrained by the known sequence of Ki-ras. Given the teachings noted above for the equivalence of the three ras genes, an ordinary practitioner would have designed probes for each gene equivalent to known working probes. Daaka discloses, on page 272, column 1, working 5' UTR probes for Ha-ras, which would direct the practitioner to design equivalent probes for Ki-ras. Ki-ras is known to be so identical to Ha-ras that they function identically and identical common mutations at codons 12 and 61 are responsible for aberrant function. Further motivation would be provided by Uhlmann, who states under the subheadings "Selection of effective target sequences" on page 576 that "As is evident from figure 47, a large number of target sequences are suitable for inhibiting gene expression. At the level of translation, these are the 5' non coding regions, the ribosome binding site, the translation start region, the coding region, and the 3' non translated region (page 576, column 1 paragraph 1)". Uhlmann explicitly directs the ordinary practitioner to the 5' UTR and the 3'UTR for selection of effective target sequences.

Reasonable expectation of success and predictability of the art

Appellant argues that the references do not provide a reasonable expectation of success for the antisense probes. Appellant argues that the references teach that testing of oligonucleotides will have to be performed for each gene. With regard to Appellant's argument on expectation of success, the MPEP 2143.02 states "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." Two references which relate to Ha-ras support the rejection on this point. Daaka, a reference in which antisense oligonucleotides were synthesized based on secondary structure considerations and tested against a closely related protein, Ha-ras, demonstrates that all three tested oligonucleotides exhibited antisense inhibitory function. This evidence supports a reasonable expectation of success, since 100% of the tested oligonucleotides met the test requirements. Saison-Behmoaras also demonstrates that antisense oligonucleotides have a reasonable expectation of success. Saison-Behmoaras shows 7 different H-ras specific antisense oligonucleotides (see page 1112, figure 1) of which 6 demonstrate acceptable antisense activity. This 85% success rate also supports the reasonable expectation of success. Appellant has provided no evidence for the allegation that synthesis of antisense oligonucleotides would lack a reasonable expectation of success. Further, Daaka, on page 267, column 1 to page 267, column 2, details eleven papers discussing successful uses of antisense oligonucleotides including three targeted against Ha-Ras. . The argument that some testing may be required to identify functional oligonucleotides does not challenge the reasonable expectation of success. Appellant has not provided evidence or sound scientific reasons

against a reasonable expectation that genes with 80% nucleotide identity and so many other similiarities would differ in sequence requirements for antisense oligonucleotides.

Apellant will later argue that the art is unpredictable because only some of the disclosed compounds are functional. Following the guidance of the prior art to make the oligonucleotides and test them is distinct from the level of effect. Appellant relies on figure 6 to show that the art is unpredictable. In fact, figure 6 shows that nearly every one of the oligonucleotides causes some level of reduction. The reason some of these were allowed is that they achieved an unexpectedly higher level of reduction. Reasonable expectation of success does not require a showing of unexpectedly better results, and appellant is confusing these two standards. Unexpected results, as shown for some of the oligonucleotides in figure 6, were found persuasive to overcome the prima facie case of obviousness. These unexpected results do not show that there is not a reasonable expectation of success and in fact, figure 6 supports an expectation of success since every oligo had some level of effect.

Secondary Considerations

Appellant then argues that a secondary consideration was found which permitted allowance of similar claims in U.S. Patent 5,872,242. The fundamental reason why the prior claims were allowed and allowable and the current claims are not is that the prior claims were commensurate in scope with a secondary consideration of unexpected results and the current claims are not commensurate in scope with the same secondary consideration of unexpected results. Thus, while the prima facie case of obviousness was maintained in U.S. Patent 5,872,242, it was overcome by a secondary consideration. A

review of the two sets of claims will show one difference between them, which is that the patented claims are drawn to oligonucleotides comprising the specified SEQ ID Nos, while the current claims are drawn to "at least an 8-nucleobase portion" of the specified SEQ ID Nos.

Appellant argues that there is no difference between the scope of these two different claims on page 10 of the response. If this argument were correct, then the claims should be subject to a statutory double patenting rejection. However, the scope of the claims is different and this difference in scope has consequences for the unexpected results demonstrated in U.S. Patent 5,872,242. The difference is the "at least an 8 nucleobase portion" comprising versus "comprising" the sequence. When the claims are "comprising" a particular sequence, the entire SEQ ID NO must be present as interpreted by the examiner. However, when the claims are drawn to a "8 nucleobase portion", then only 8 nucleobases of the SEQ ID NO must be present.

So this difference in scope directly impacts the secondary consideration of unexpected results. While the particular sequence of SEQ ID NO: 20 (among several others) was found to have the unexpected result (as noted in the reasons for allowance attached by Appellant as exhibit 3) of reducing Ras expression, the reasons for allowance expressly noted that other oligonucleotides selected from other regions did not yield equivalent reductions. As MPEP 716.02(d) notes "the objective evidence of nonobviousness must be

commensurate in scope with the claims which the evidence is offered to support." In the current case, appellant is claim a much broader genus which is any 8 nucleotide region

selected from, for example, SEQ ID NO: 20, for which no objective evidence of nonobviousness is shown which is commensurate in scope with this broader genus. For example, SEQ ID NO 20 is CTGCCTCCGCCGCCGCGGCC. Some of the 8-mers from SEQ ID NO 20 are CTGCCTCC, CCTCCGCC or CCGCGGCC. However, the claim encompasses not just the particular 8-mers but sequences of up to 30 nucleotides comprising them. So this genus, which appellant claims is commensurate in scope with the unexpected result, incorporates more than 4^{22} different possible antisense molecules for each different 8-mer. A showing that an oligonucleotide comprising SEQ ID NO: 20 has an unexpected result does not carry over to a showing that each of the 4^{22} different possible antisense molecules has the same unexpected result. Some of them may, but the evidence showing that one member out of 4^{22} different possible probes is not commensurate in scope.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

December 6, 2001

JEFFREY FREDMAN
PRIMARY EXAMINER

Conferees

Gary Benzion, SPE 1637

George Elliott, SPE, Biotechnology Practice Specialist

CONFEREE

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600